The following full text is a publisher’s version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/174446

Please be advised that this information was generated on 2018-03-09 and may be subject to change.
Tuberculous meningitis (TBM) remains a major cause of death and disability in tuberculosis-endemic areas, especially in young children and immunocompromised adults. Research aimed at improving outcomes is hampered by poor standardization, which limits study comparison and the generalizability of results. We propose standardized methods for the conduct of TBM clinical research that were drafted at an international tuberculous meningitis research meeting organized by the Oxford University Clinical Research Unit in Vietnam. We propose a core dataset including demographic and clinical information to be collected at study enrollment, important aspects related to patient management and monitoring, and standardized reporting of patient outcomes. The criteria proposed for the conduct of observational and intervention TBM studies should improve the quality of future research outputs, can facilitate multicenter studies and meta-analyses of pooled data, and could provide the foundation for a global TBM data repository.

**Keywords.** tuberculous meningitis; research methods; clinical research; core dataset

Tuberculous meningitis (TBM) was almost universally fatal until the first antibiotic treatment with streptomycin and isoniazid became available [1]. TBM remains a major cause of disease, disability, and death in tuberculosis-endemic areas, but research aimed at improving outcomes is hampered by difficulties in patient recruitment and heterogeneous research methodology. The development of a consensus TBM case definition for use in TBM research has assisted new diagnostic studies by providing a uniform reference standard [2]. However, variable data collection methods, different disease classification systems, and the absence of standardized outcome assessment continue to limit study comparison and complicate efforts to perform systematic reviews and meta-analyses.

The need to standardize clinical trial endpoints is well recognized for pulmonary and drug-resistant tuberculosis research and is the focus of several international consortia (eg, PreDICT-TB [www.predict-tb.eu], RESIST-TB [www.resisttb.org], and TREAT-TB [www.treattb.org]). Core research methods have been proposed for adults and children with multidrug-resistant tuberculosis [3, 4]. In this context, the Oxford University Clinical Research Unit in Vietnam, together with the University of Cape Town’s Clinical Infectious Diseases Research Initiative, organized a meeting of international TBM researchers in Dalat, Vietnam (20–22 May 2015) to assess recent progress and address key challenges in TBM research. Researchers actively engaged in TBM research worldwide were invited with the aim of creating an international consortium that could make recommendations concerning the objectives and methodology of future TBM clinical research.

A TBM research methodological framework was discussed and agreed upon during the meeting by all delegates, broadly defining the key baseline, treatment, and outcome data required in the conduct of TBM research. Thereafter, proposed essential and desirable data were circulated by the lead authors (B. J. M., A. D. H., and G. E. T.) and agreed or adapted by the writing committee (all listed authors) until consensus was found. A statement thereby arose from the meeting, proposing standardized criteria for the conduct and reporting of TBM research and shared data collection templates. We provide an overview of the consensus reached by the consortium, identifying demographic and clinical information to be collected at study enrollment, important aspects related...
to patient management and monitoring, and standardized reporting of patient outcomes. Specific data points were categorized as either essential or desirable. The essential data points are intended to define minimum criteria for the conduct of both observational and intervention studies, and to identify a core dataset for universal use in future clinical research. Better-harmonized research methods would improve the quality of research outputs and facilitate study comparisons and, in the future, may provide the foundation for a global TBM data repository.

**COHORT DESCRIPTION AND METHODS**

Adequate cohort description with clarification of the clinical “point of entry” is essential to ensure study reproducibility and to interrogate differences in study outcomes that may be unrelated to the intervention studied. Because treatment outcomes and diagnostic test performance may vary according to the severity of disease, age, immune status, and patient management, the study population must be well characterized in terms of setting, inclusion criteria, demographics, human immunodeficiency virus (HIV) infection and immune status, disease classification, and treatment received.

**INFORMATION TO COLLECT AT ENROLLMENT**

Table 1 provides a summary of essential and desirable baseline information to be collected at study enrollment. Essential data points include information required by the previously published uniform TBM research case definition (Table 2) [2], which should be applied to ensure adequate diagnostic workup and to characterize the study cohort in a standardized fashion. For diagnostic studies, it is important to ensure that control subjects represent a credible clinical entry point for TBM diagnostic evaluation, to assess “real-life” diagnostic accuracy.

**Disease Severity and Phenotype**

Given the diversity of clinical presentation and disease severity, it is important to grade TBM severity in a pragmatic and standardized fashion. As a minimum, HIV status (preferably with CD4 count and World Health Organization [WHO] clinical disease staging) must be recorded and the modified British Medical Research Council (BMRC) TBM grade should be ascertained in all studied patients before the start of treatment. BMRC investigators [1] first graded TBM patients as “early” (no clinical signs of meningitis or focal neurology and fully conscious); “medium” (patient’s condition falling between early and advanced); and “advanced” (extremely ill, in deep coma). With the introduction of the Glasgow Coma Scale (GCS) in 1974 [5], this was modified as grade I (GCS 15; no focal neurological signs), grade II (GCS 11–14, or 15 with focal neurological signs), and grade III (GCS ≤10) disease [6]. Numerous studies across all age groups have shown that the modified BMRC grade is a strong independent predictor of outcome [6–10]. TBM patients with grade I disease are often underrepresented in studies, as their nonspecific symptoms may not trigger a lumbar puncture, which usually provides the entry point for TBM studies. Subdivision of grade II disease has been proposed [11], as have other prognostic systems based on weighted scoring of mental status, seizures, cranial nerve palsies, motor deficit, and tone [12], but these have not been validated. Because level of consciousness is influenced by rapidly reversible raised intracranial pressure and electrolyte disturbances, it is important to repeat the BMRC disease severity grading 7 days after TBM treatment initiation. This provides a useful reassessment of disease severity that may be better associated with long-term outcome than a single baseline assessment.

**Baseline Investigations**

Essential and desired study investigations, to be performed at enrollment, are summarized in Table 1. Cerebrospinal fluid (CSF) sampling and analysis are essential to assist diagnostic workup and cohort description and to define prognosis. Low CSF white blood cell count, low glucose, and high lactate have been associated with death in studies from Vietnam [13]. In HIV-coinfected patients, baseline CSF neutrophil count and culture positivity for *Mycobacterium tuberculosis* are predictive of TBM immune reconstitution inflammatory syndrome (IRIS) [14]. Cryptococcal meningitis and TBM have similar presenting features and CSF cryptococcal antigen tests should be performed, especially in those with advanced HIV infection (peripheral CD4+ count <100 cells/µL), in whom both diseases are common. Peripheral blood findings have limited diagnostic or prognostic value, but it is important to document anemia, determine baseline renal and liver function tests for drug toxicity monitoring, and assess HIV and immune status. Hyponatremia has been linked to a worse outcome [15], while in HIV-1–coinfected patients lower blood hematocrit [13] and low CD4+ T-cell count [16, 17] have been associated with death.

Brain computed tomography (CT) with or without contrast and magnetic resonance imaging (MRI) characterize the pathological processes underlying the clinical presentation, disease course, and long-term consequences of TBM. Baseline brain imaging is recommended for all patients, although this may not be available in all settings [18]. Classic imaging findings include basal meningeal enhancement, hydrocephalus, tuberculomas, and cerebral infarction [19]. MRI is more sensitive in detecting early ischemia and brainstem lesions [20]. TBM-related infarcts are most commonly located in the territories of the proximal middle cerebral artery and the medial lenticulostriate and thalamoperforating vessels [21, 22]. Brain imaging provides a window on the pathophysiology of TBM, and standardized documentation of these complications and their response to treatment could improve management and may suggest new therapeutic approaches.
Sample Collection and Laboratory Methods

Diagnostic yield is influenced by both the type and quality of specimens collected; therefore careful description of specimen collection methods and test procedures are important. Microbiological yield is affected by CSF volume, sample transport delays, and processing techniques [23]. The CSF sample volume used for each mycobacterial diagnostic test should be reported. In addition, adequate quality assurance of all research laboratories is essential to ensure test reliability.

Table 1. Baseline Information to Be Collected at Enrollment in Tuberculous Meningitis Studies

<table>
<thead>
<tr>
<th>Information</th>
<th>Essential</th>
<th>Desirable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Age (date of birth)</td>
<td>Sex</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Neurological symptoms (headache, vomiting, convulsions)—duration(^\text{a})</td>
<td>Systemic symptoms (weight loss, night sweats, cough, fever)—duration(^\text{a})</td>
</tr>
<tr>
<td>Medical history</td>
<td>Previous and/or current TB</td>
<td>Previous TB preventive therapy</td>
</tr>
<tr>
<td></td>
<td>HIV infection/ART</td>
<td>Diabetes (use of insulin)</td>
</tr>
<tr>
<td></td>
<td>In children</td>
<td>BCG vaccination/scar</td>
</tr>
<tr>
<td></td>
<td>Recent TB contact(^\text{b})</td>
<td></td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Weight (true or estimated)</td>
<td>Height</td>
</tr>
<tr>
<td></td>
<td>Glasgow Coma Scale score(^\text{a})</td>
<td>Convulsions (focal or generalized)</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve palsy or other focal neurological deficit (specify)(^\text{a})</td>
<td>Papilledema or other signs of raised intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>In children</td>
<td></td>
</tr>
<tr>
<td>Laboratory investigations</td>
<td>CSF</td>
<td>CSF Collection site (lumbar, ventricular)</td>
</tr>
<tr>
<td></td>
<td>Appearance(^\text{a})</td>
<td>Volume (for TB investigations)</td>
</tr>
<tr>
<td></td>
<td>Total and differential WBC count(^\text{a})</td>
<td>ZN stain(^\text{d})</td>
</tr>
<tr>
<td></td>
<td>Protein and glucose(^\text{a})</td>
<td>Lactate</td>
</tr>
<tr>
<td></td>
<td>India ink stain (and/or cryptococcal antigen)(^\text{a})</td>
<td>Opening pressure</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial culture (and/or NAAT) and drug susceptibility testing(^\text{a,d})</td>
<td>Additional tests to exclude alternative diagnoses (eg, bacterial and fungal culture, enterovirus PCR)</td>
</tr>
<tr>
<td></td>
<td>Extraneural samples</td>
<td>IGRA or TST (adults)</td>
</tr>
<tr>
<td></td>
<td>ZN stain(^\text{e}), Mycobacterial culture (and/or NAAT)(^\text{a,d})</td>
<td>Hepatitis B or C coinfection</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood</td>
<td>Syphilis serology</td>
</tr>
<tr>
<td></td>
<td>FBC with differential WBC count</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma glucose (paired with CSF), sodium, potassium, urea, and creatinine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver aminotransferases (AST, ALT baseline)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>Chest radiograph</td>
<td>Imaging MRI/CT/ultrasound of extraneural sites suspected of TB disease(^\text{a})</td>
</tr>
<tr>
<td></td>
<td>Signs of active TB; miliary appearance</td>
<td>Air encephalogram to differentiate communicating and noncommunicating hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Brain CT or MRI(^\text{a})</td>
<td>Hydrocephalus description; presence of pterventricular edema; herniation</td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus; basal meningeal enhancement, infarct, tuberculosis</td>
<td>Infarct; type; single/multiple; anatomical location</td>
</tr>
<tr>
<td>Diagnostic certainty and</td>
<td>Definite, probable, possible or not TBM(^\text{a})</td>
<td>CD4 count (most recent and nadir)</td>
</tr>
<tr>
<td>disease severity</td>
<td>BMRC TBM severity grade(^\text{e}) (1, 2, or 3)</td>
<td>HIV RNA load (most recent and highest)</td>
</tr>
<tr>
<td>If HIV infected</td>
<td>WHO clinical disease staging</td>
<td>Detail of ART regimen</td>
</tr>
<tr>
<td></td>
<td>CD4 count</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ART</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMRC, British Medical Research Council; CSF, cerebrospinal fluid; CT, computed tomography; FBC, full blood count; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; MRI, magnetic resonance imaging; NAAT, nucleic acid amplification test (including GeneXpert MTB/RIF); PCR, polymerase chain reaction; TB, tuberculosis; TBM, tuberculous meningitis; TST, tuberculin skin test; WBC, white blood cell; WHO, World Health Organization; ZN, Ziehl-Neelsen.

\(^{a}\)Data required for uniform TBM research case definition criteria (Table 2).

\(^{b}\)Close/household contact with an infectious (pulmonary) TB case during the past year.

\(^{c}\)The yield of CSF ZN microscopy is so low that many laboratories do not offer this as a routine test.

\(^{d}\)Genotypic (at least GeneXpert MTB/RIF) or phenotypic drug susceptibility testing must be performed if Mycobacterium tuberculosis is detected.

\(^{e}\)According to modified BMRC criteria.
**Table 2. Uniform Tuberculous Meningitis Research Case Definition Criteria[2]**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical criteria (maximum category score = 6)</td>
<td></td>
</tr>
<tr>
<td>Symptom duration of &gt;5 d</td>
<td>4</td>
</tr>
<tr>
<td>Systemic symptoms suggestive of TB (≥1): weight loss/poor weight gain</td>
<td>2</td>
</tr>
<tr>
<td>Children, night sweats, or persistent cough &gt;2 wk</td>
<td>2</td>
</tr>
<tr>
<td>History of recent close contact with an individual with pulmonary TB or</td>
<td>2</td>
</tr>
<tr>
<td>a positive TST/GRA in a child aged &lt;10 y</td>
<td></td>
</tr>
<tr>
<td>Focal neurological deficit (excluding cranial nerve palsies)</td>
<td>1</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>1</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>1</td>
</tr>
<tr>
<td>CSF criteria (maximum category score = 4)</td>
<td></td>
</tr>
<tr>
<td>Clear appearance</td>
<td>1</td>
</tr>
<tr>
<td>Cells: 10–500×10⁶/L</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocytic predominance (&gt;50%)</td>
<td>1</td>
</tr>
<tr>
<td>Protein concentration &gt;1 g/L</td>
<td>1</td>
</tr>
<tr>
<td>CSF to plasma glucose ratio of &lt;50% or an absolute CSF glucose concentration &lt;2.2 mmol/L</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral imaging criteria (maximum category score = 6)</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus (CT and/or MRI)</td>
<td>1</td>
</tr>
<tr>
<td>Basal meningeal enhancement (CT and/or MRI)</td>
<td>2</td>
</tr>
<tr>
<td>Tuberculosis (CT and/or MRI)</td>
<td>2</td>
</tr>
<tr>
<td>Infarct (CT and/or MRI)</td>
<td>1</td>
</tr>
<tr>
<td>Precontrast basal hyperdensity (CT)</td>
<td>2</td>
</tr>
</tbody>
</table>

**Clinical criteria:**
- Symptom duration of >5 d
- Systemic symptoms suggestive of TB (≥1): weight loss/poor weight gain in children, night sweats, or persistent cough >2 wk
- History of recent close contact with an individual with pulmonary TB or a positive TST/GRA in a child aged <10 y
- Focal neurological deficit (excluding cranial nerve palsies)
- Cranial nerve palsy
- Altered consciousness

**CSF criteria:**
- Clear appearance
- Cells: 10–500×10⁶/L
- Lymphocytic predominance (>50%)
- Protein concentration >1 g/L
- CSF to plasma glucose ratio of <50% or an absolute CSF glucose concentration <2.2 mmol/L

**Cerebral imaging criteria:**
- Hydrocephalus (CT and/or MRI)
- Basal meningeal enhancement (CT and/or MRI)
- Tuberculosis (CT and/or MRI)
- Infarct (CT and/or MRI)
- Precontrast basal hyperdensity (CT)

**Exclusion of alternative diagnoses:**
An alternative diagnosis must be confirmed microbiologically, serologically, or histopathologically.

**Definite TBM:**
- AFB seen on CSF microscopy, positive CSF M. tuberculosis culture, or positive CSF M. tuberculosis commercial NAAT in the setting of symptoms/signs suggestive of meningitis; or
- AFB seen in the context of histological changes consistent with TB brain or spinal cord together with suggestive symptoms/signs and CSF changes, or visible meningitis (on autopsy).

**Probable TBM:**
- Total score of ≥12 when neuroimaging available or total score of ≥10 when neuroimaging unavailable. At least 2 points should either come from CSF or cerebral imaging criteria.

**Possible TBM:**
- Total score of 6–11 when neuroimaging available, or total score of 6–9 when neuroimaging unavailable.

**Abbreviations:**
AFB, acid-fast bacilli; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; IGRA, interferon-γ release assay; MRI, magnetic resonance imaging; NAAT, nucleic acid amplification test; TB, tuberculosis; TBM, tuberculous meningitis; TST, tuberculin skin test; US, ultrasound.

**Antituberculosis Drug Treatment**

As summarized in Table 3, it is essential to document the dose, route of administration, and duration of all antituberculosis drugs used in TBM treatment. Antituberculosis drug-related adverse events are more important in the treatment of TBM than other forms of tuberculosis because treatment interruptions have been independently associated with death [24]. Drug-induced liver injury (DILI) is the commonest adverse event and should be documented alongside changes in antituberculosis drug regimen. Outstanding questions remain concerning optimal management when DILI occurs, and harmonized data collection would allow analyses to address these.

When performing antituberculosis drug treatment trials, it is important to document drug quality as this can be highly variable. WHO-prequalified drugs have been rigorously evaluated and meet strict quality criteria (a list of prequalified drugs is available at [http://apps.who.int/prequal/query/ProductRegistry.aspx](http://apps.who.int/prequal/query/ProductRegistry.aspx)). For other drugs, pharmaceutical companies should provide "certificates of analysis" and data on bioequivalence.

**Pharmacokinetic/Pharmacodynamic Substudies**

Pharmacokinetic/pharmacodynamic (PK/PD) substudies can help to explain trial findings and provide important dosing information for future studies. Evaluation of individual exposures achieved provides insight into predictors of drug exposure and enables concentration-response relationships (PK/PD analysis) to be established [25–27]; the latter may reveal exposure thresholds predictive of good treatment outcome or drug toxicity [26, 28, 29]. Pharmacokinetic analysis should ideally include both plasma and CSF measurements, although CSF concentrations may not reflect the brain tissue concentration of highly lipophilic drugs [30, 31]. Pharmacokinetic studies often take place at "steady state," when the processes of accumulation or induction are complete (if rifampicin this can take up to 10 days), but in TBM we suggest measuring exposures during the critical first days of treatment when mortality is highest [27]. CSF sampling after weeks of treatment may yield different results, as CSF drug penetration may reduce as meningeal inflammation lessens.

The standard method to assess CSF penetration is the CSF to plasma ratio for total drug exposure (area under the concentration-time curve [AUC]) during the dosing interval, which requires multiple plasma and CSF samples [25]. Alternatively, a CSF to plasma concentration ratio can be established by a single point measurement, but this is time dependent as the ratio is often variable over the dosing interval [31]. Although single time point CSF to plasma ratios should be interpreted with caution, pharmacokinetic modeling may approximate the CSF to plasma AUC ratio despite limited sampling, if such sampling takes place at multiple time points. It is important that CSF to plasma concentration ratios should be based upon estimated protein-unbound ("free") exposure measures. In plasma, only the protein-unbound fraction is active and able to penetrate...
into the CSF. If a drug with high protein binding in plasma has excellent CSF penetration, a CSF to plasma ratio based on protein-unbound concentrations would be close to unity. In contrast, a ratio based on total (bound + unbound) concentrations would incorrectly suggest poor penetration [31], as is the case with rifampicin. Therefore, a correction for protein binding of plasma concentrations should always be made [25, 26].

Pharmacokinetic sampling can be “intensive” or “sparse,” or ideally a mixture of both to assist accurate modeling. Analytical methods used to determine drug concentrations should have appropriate intralaboratory (internal) assessment of accuracy, precision, and other validation measures. Participation in an interlaboratory (external) proficiency testing program is recommended [32]. Of note, CSF drug concentrations cannot be measured using plasma assays without careful validation.

**Adjunctive Anti-inflammatory Therapy**

TBM studies should describe the type, dose, route of administration, and duration of anti-inflammatory therapy used (Table 3). Adjunctive corticosteroids are currently recommended for all HIV-uninfected TBM patients during the first 6–8 weeks of treatment [9]; they are also used in HIV-infected patients, although the evidence of benefit is much less clear.

Corticosteroids are also often used for the management of tuberculomas and IRIS in HIV-infected patients, although the evidence base is weak. Some patients who do not respond to corticosteroids may benefit from other agents, such as thalidomide or anti–tumor necrosis factor-α biologic agents [33–36]. Two small studies also suggest that aspirin may reduce cerebral infarcts [37, 38], but this has not been confirmed in larger-scale studies.

**Management of Hydrocephalus**

As a minimum, the presence of hydrocephalus assessed by brain CT or MRI should be documented at the start of treatment. An assessment of whether the hydrocephalus is communicating or noncommunicating is desirable, and the management (medical or surgical) should be documented (Table 3). Raised intracranial pressure, largely due to hydrocephalus, is a common problem in patients with TBM [10, 39]. If untreated, hydrocephalus can exacerbate the cerebral ischemia caused by perfusion-limiting vasculitis, which is a key feature of TBM. Untreated hydrocephalus is independently associated with death [40, 41]. Whether the hydrocephalus is communicating or noncommunicating [10, 42] has important management implications. At present, the only way to reliably differentiate communicating from noncommunicating...
At presentation / Diagnosis
- Demographics, medical history, presenting symptoms and signs
- Cerebrospinal fluid analysis and mycobacterial culture & DST
- Other laboratory investigations (LFTs), brain imaging (Table 1)
- Assess diagnostic certainty (Table 2) & BMRC severity grade (Figure 2)
- HIV test all; if infected: CD4 count, viral load, ART

During the first month
- Day 7 BMRC TBM severity grade
- Conscious level and new neurological events (Table 3)
- Anti-TB drug treatment, anti-inflammatory treatment, hydrocephalus management, ART (Table 3)
- Relevant blood tests as required (at least once/week)
- Cerebrospinal fluid analysis if diagnostic uncertainty/poor treatment response
- Serious adverse events

Beyond the first month
- New neurological events (Table 3)
- Anti-TB treatment, anti-inflammatory treatment, hydrocephalus management, ART (Table 3)
- Monthly conscious level
- Relevant blood tests as required (at least once/month)
- Serious adverse events

12 months from TB treatment initiation
- Death and disability (Table 4)
- Time to hospital discharge
- New neurological events
- Serious adverse events
- For HIV-infected patients: new stage 4 illnesses, TBM-IRIS

Figure 1. Proposed minimum schedule of investigations and outcome measurements in studies of tuberculosis meningitis. Abbreviations: ART, antiretroviral therapy; BMRC, British Medical Research Council; DST, drug susceptibility testing; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; LFTs, liver function tests; TBM, tuberculous meningitis.

hydrocephalus is with an air encephalogram or using contrast ventriculography [43, 44]. Performing an air encephalogram does not require any special resources and can be performed when collecting a CSF sample. Ventricular shunting is usually indicated for noncommunicating hydrocephalus, while a combination of diuretics (acetazolamide and furosemide) may treat communicating hydrocephalus [45]; the value of this approach requires further confirmation in adults.

General Supportive Care
The provision of optimal supportive care in patients with TBM is rarely reported and often neglected and is therefore highlighted here. Hyponatremia occurs in a high percentage of TBM patients, is associated with poorer outcome [10], and should be documented (Table 3). Hyponatremia may result from inappropriate antidiuretic hormone secretion or cerebral salt wasting or may represent an appropriate compensatory response to maintain cerebral perfusion. Plasma sodium concentrations should be recorded at baseline and through the early phase of hospital treatment. In critically ill patients, changes in cerebral perfusion and oxygenation are highly dynamic, but can be captured through continuous intracranial monitoring. This is invasive and only possible during intensive care admission in settings where such facilities exist. Transcranial Doppler [46] and near-infrared spectroscopy provide less-invasive alternatives, but these methods require more rigorous validation and have not yet demonstrated clinical utility. Simple measures to reduce cerebral ischemia and brain cell metabolic stress include maintaining adequate blood pressure and glucose levels, providing supplemental oxygen, and controlling fever [47]. These parameters should be recorded in all critically ill patients (Table 3).

OUTCOME MEASURES
The inconsistent reporting of outcome measures limits critical study evaluation and comparison. TBM is associated with high mortality; therefore, death is an essential outcome measure. The time of death in relation to the start of antituberculosis treatment should also be documented, and we recommend reporting to at least 12 months from antituberculosis treatment initiation. Cause of death is notoriously difficult to determine without formal postmortem examination, but deaths directly attributable to TBM are more likely to occur in the first 3 months of treatment; later deaths may be caused by secondary infections, for example, especially in those left with severe neurological disability. An assessment by the attending physician as to the likely cause of death (TBM attributable/not attributable) is desirable but not essential, given the inherent limitations of this approach.

The reporting of functional outcomes are also essential, but different measures are used [9], and detailed neurocognitive outcomes are rarely assessed [48]. Given the importance of neurodisability and comparable outcome measurement, we recommend that the Modified Rankin Score should be recorded 12 months from antituberculosis treatment initiation in all adults and in children. The score (detailed in the Supplementary Appendix) assesses whether or not the subject can live independently of others. We also recommend recording the Pediatric Version of the Glasgow Outcome Scale–Extended (GOS-E peds) in children (Table 4); however, this scale, created for children following neurotrauma, needs further validation in childhood TBM.

TBM causes significant long-term neurocognitive impairment in children [10, 49] and adults [7], and detailed neurocognitive and psychiatric outcomes should be reported where possible. The Griffiths Mental Developmental Scales or the Pediatric Cerebral Performance Category Scale provide assessment on age-appropriate neurocognitive and developmental...
outcomes. It is important that children are compared to age-matched controls from the same socioeconomic background, given major environmental influences on early cognitive development.

Paradoxical Reactions

Clinical deterioration after the start of antituberculosis treatment—commonly called paradoxical reactions and associated with increased intracerebral inflammation—occurs in approximately 30% of HIV-uninfected individuals with TBM [50] and around 50% of those who are HIV infected [14]. Paradoxical reactions are associated with new or worsening intracerebral tuberculomas, hydrocephalus, infarcts, and/or spinal radiculomyelitis. In HIV-infected subjects recently started on antiretroviral therapy, these events may be defined as TBM-IRIS following the International Network for the Study of HIV-Associated IRIS criteria [51], modified for TBM.

All suspected paradoxical reactions and their timing with respect to antituberculosis drug initiation should be recorded (Table 4). When possible, providers should investigate all suspected paradoxical reactions with brain imaging and document the findings, management given, and outcomes. Alternative causes that should be excluded as far as possible include drug resistance, poor adherence to treatment, drug-related adverse events, and other opportunistic infections. We also recommend that all WHO HIV stage 4 illnesses should be recorded throughout the course of TBM treatment (Table 4).

PROPOSED CORE DATASET

Participants at the workshop reinforced calls for standardized approaches, including laboratory and clinical assessment procedures and data reporting. All laboratory tests should be guided by detailed standard operating procedures, including sample collection, processing, transport, storage, and laboratory procedures for specific diagnostic tests, including quality assurance measures; relevant standard operating procedures are included in the Supplementary Data. Demographic and clinical data should also be collected in a standardized fashion. The essential elements listed in the tables provide the basis for a core dataset that represents the minimum data to be captured in future TBM studies. A proposed data capture form that includes all the proposed “essential” and “desirable” variables (Tables 1–4) is included in the Supplementary Data.

CONCLUSIONS

Developing standardized approaches represents a critical first step to establish the evidence base required to improve TBM detection and outcome. Poor study comparability due to variable methods, case definitions, and data collection and reporting highlight the inadequacy of current approaches. Wide adoption of the standard methods proposed here should help to move the field forward and ensure that the benefits of technological advances are fully realized. This document should be viewed as a living tool that will be refined as the evidence base and field experience with conducting multicenter TBM studies grow and are critically evaluated at future meetings.
Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Acknowledgments. The Tuberculous Meningitis International Meeting was convened by the Oxford University Clinical Research Unit in Vietnam and the Clinical Infectious Diseases Research Initiative of the University of Cape Town, with support from the Li Ka Shing Foundation and Wellcome Trust, UK.

Potential conflicts of interest. All authors: No potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


**Tuberculous Meningitis International Research Consortium Members**

Rob Aarnoutse, Radboud University Medical Center, Nijmegen, The Netherlands; Nate Bahr, University of Minnesota; David Boulware, University of Minnesota; Maxine Caws, Liverpool School of Tropical Medicine, UK; Mark Cronan, Duke University School of Medicine, Durham, North Carolina; Sofiati Dian, Radboud University Medical Center, Indonesia; Kelly Dooley, Johns Hopkins University School of Medicine, Baltimore, Maryland; Sarah Dunstan, University of Melbourne, Australia; Guo-dong Feng, Fourth Military Medical University, China; Anthony Figaji, University of Cape Town, South Africa; Ahmad Rizal Ganiem, Universitas Padjadjaran Bandung, Indonesia; Ravindra Kumar Garg, King George Medical University, Lucknow, India; Mudit Gupta, Fortis Memorial Research Institute, Gurgaon, India; Rakesh K. Gupta, Fortis Memorial Research Institute, Gurgaon, India; Sneha Gupta; University of California, San Francisco; Dorothee Heemskerk, Oxford University Clinical Research Unit, Vietnam; Jayantee Kalita, Sanjay Gandhi Postgraduate Institute of Medical Sciences (PGIMS), Lucknow, India; Rachel Lai, The Francis Crick Institute, London, UK; Ben Marais, University of Sydney, Australia; Suzaan Marais, University of Cape Town, South Africa; Helen McIloron, University of Cape Town, South Africa; Graeme Meintjes, University of Cape Town, South Africa; Usha K. Misra, Sanjay Gandhi PGIMS, Lucknow, India; Bang Duc Nguyen; Pham Ngoc Thach Hospital for Tuberculosis and Lung Diseases, Vietnam; Mai Thi Hoang Nguyen, University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam; Thuong Thuy Thuong Nguyen, Oxford University Clinical Research Unit, Vietnam; Yen Bich Nguyen, Pham Ngoc Thach Hospital for Tuberculosis and Lung Diseases, Vietnam; Vinod B Patel, University of KwaZulu-Natal, South Africa; Thomas Pouplin, Mahidol-Oxford Tropical Medicine Research Unit, Thailand; Lalita Ramakrishnan, University of Cambridge, UK; Ursula Rohlwink; University of Cape Town, South Africa; Rovina Ruslami, Universitas Padjadjaran, Bandung, Indonesia; Rada Savic, University of California, San Francisco; Johan Schoeman, University of Stellenbosch, South Africa; James Seddon, Imperial College, London, UK; Javeed Shah, University of Washington, Seattle; Xiaodan Shi, Fourth Military Medical University, China; Regan Solomons, Stellenbosch University, South Africa; Vijay Srinivasan, Oxford University Clinical Research Unit, Vietnam; Guy Thwaites, Oxford University Clinical Research Unit, Vietnam; David Tobin, Duke University School of Medicine, Durham, North Carolina; Tram Thi Bich Tran, Oxford University Clinical Research Unit, Vietnam; Thinh Thi Van Tran, Oxford University Clinical Research Unit, Vietnam; Mai Quynh Trinh, University of Sydney, Australia; Jaya Sivaswami Tyagi, All India Institute of Medical Sciences, New Delhi, India; Reinout van Crevel, Radboud University Medical Center, Nijmegen, The Netherlands; Arjan van Laarhoven, Radboud University Medical Center, Nijmegen, The Netherlands; Ronald van Toorn, Tygerberg Children’s Hospital and Stellenbosch University, South Africa; Douwe Visser, VU University Medical Center Amsterdam, The Netherlands; Robert J. Wilkinson, Imperial College, London and Francis Crick Institute, UK and University of Cape Town, South Africa; Marcel Wolbers, Oxford University Clinical Research Unit, Vietnam.